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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/719,662 | 11/21/2003 | Sonia Vadrucci | 126442-100010-US | 1323 |

34026 7590 07/20/2006

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| EXAMINER | |
|---|---|
| SCHNIZER, RICHARD A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/719,662 | VADRUCCI ET AL. | |
| | Examiner | Art Unit | |
| | Richard Schnizer, Ph. D | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *17-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

An amendment was received and entered on 5/11/06.

Applicant's election with traverse of group 1 is acknowledged. Traversal is on the grounds that restriction between claims 36 and 37 is improper, restriction between diseases treatable by the same invention is improper, and the contention that there is no undue search burden imposed by searching the different inventions. The Examiner agrees that restriction between claims 36 and 36 would be improper. In fact, there is no restriction between claims 36 and 37. Claim 37 was restricted into 9 inventions that are linked by claim 36. Should claim 36 be found allowable, then all of the inventions of claim 37 will be rejoined, as discussed at page 3 of the restriction requirement. Applicant's argues that restriction of claim 37 into methods of treating different diseases treatable by the same invention is improper, indicating that fusogenic vesicles and their preparation or use constitute the claimed invention, and not the condition treated or prevented. This is unpersuasive. Applicant is reminded that the invention is *what is claimed*. Claim 37 is drawn to methods of treating at least 9 types of unrelated diseases and disorders. This requires search and consideration of the enablement of treating each unrelated type of disease or disorder. Such a search clearly involves a different field of search for each type of disease, so the Examiner has clearly met the burden imposed by MPEP 808.02. Furthermore, as the Examiner understands the invention, the fusogenic vesicle itself is not the essential feature that is required for treating a disease. That essential feature would be a therapeutic or immunologically active substance with some correlation to the disease. As a result, the search referred

to by Applicant would embrace the entire scope of recited diseases as well as the nature of any correlative therapeutic or immunologically active substances, and their ability to be delivered by fusogenic vesicle to achieve the desired effect. This represents an undue burden, and the restriction requirement is maintained and made FINAL.

***Comment***

Claim 13 would be clearer if virosomal lipids were derived "from a virus selected from the group comprising influenza virus, VSV, SFV, and HIV". As currently written, the claim implies that influenza, VSV, SFV, and HIV are lipids.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 and 38 are indefinite because it is unclear what is intended by "distinct fusion characteristics" because it is unclear from what the fusion characteristics must be distinct. The claim could be interpreted as requiring more than one type of fusion protein, wherein the different types have different fusion characteristics.

Alternatively, the claim could be interpreted more broadly to require more than one fusion protein of a single type that has detectable ("distinct") fusion characteristics.

Claims 3 and 4 are indefinite because they recite "the encapsulated therapeutic or immunologically active substance" without antecedent basis. Claim 1 does not require encapsulation of any substance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 11-16, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the genus of fusion proteins or peptides with "distinct fusion characteristics." This limitation can be interpreted as requiring fusion proteins or peptides with fusion characteristics that are distinct from each other. To the extent that this interpretation is applied, the claims lack an adequate written description.

Claims 7-9 require that the fusion proteins are derived from viruses. No other claim is limited to virus-derived fusion proteins. The specification at paragraph 21 on page 8 defines the term "fusion protein" as referring to peptides or proteins capable of inducing and/or promoting a fusion reaction between a fusogenic vesicle membrane and

a biological membrane of the target cell. The specification fails to disclose by complete structural description, drawings, or relevant identifying characteristics any non-viral fusion peptide or protein. As such one of skill in the art could not conclude that Applicant was in possession of this genus of fusion proteins at the time of the invention. It follows that Applicant was not in possession of non-viral fusion proteins that were distinguished from each other by differing sensitivities to temperature, ion concentration, acidity, cell type, or tissue type, as required by instant claims 5 and 6.

With regard to the genus of viral fusion proteins, a search of the prior art shows a variety of viral fusion proteins were known having differing pH optima such that this subgenus of the claimed invention is considered to be adequately described.

With regard to temperature sensitivity, the specification teaches that hemagglutinin (HA) from influenza virus strain X-31 allows fusion at low temperature (e.g. 5°C), whereas HAs from strains PR8/34 or A/Singapore require temperatures of at least 25°C. A search of the prior art indicates that fusion activity generally increases with temperature from subphysiological temperatures into the physiological range. The specification discloses no example of any fusion protein, other than influenza X-31 HA, that is distinguished by its sensitivity to temperature. The disclosure of only a single virus fusion protein that is distinguishable from other virus fusion proteins by temperature sensitivity is not considered to be a disclosure of a representative number of species of the genus, and the specification fails to disclose any relevant identifying characteristics of the genus, such as a correlation between structure and function that would imply possession of the genus.

The specification discloses no fusion proteins that are distinguished by sensitivity to ion concentration (other than $H^+$), cell type, or tissue type, nor does the specification disclose any relevant identifying characteristics of such proteins. The specification states at paragraph 26 on page 10 that "other fusion proteins with distinct fusion characteristics, including sensitivity to temperature, ion concentration, acidity, cell type and tissue type specificity, etc. are well known in the art and may be used for the purposes of the present invention. Fusion proteins with different fusion characteristics can be derived from different influenza strains, such as MRC-1, X-97, NIB24, NIB26, X-47, A/Johannesburg/33 and A/Singapore, to name a few." A search of the Medline, Caplus, Embase, Biosis, and Scisearch databases revealed showed that X-47 is recognized as having negligible fusion activity below 20° C, with a pH optimum of 5.6, and that a wide variety of viruses are known with different pH optima for fusion. However, no information on the fusion sensitivities of any of the other recited viruses was found, and it is unclear form the specification which of the various distinguishing characteristics were to be attributed to which of the recited viruses. As a result, the specification fails to disclose fusion proteins that are distinguished by sensitivity to ion concentration (other than $H^+$), cell type, or tissue type.

In summary, considering the disclosure of the specification as a whole, and the state of the art at the time of the invention, one of skill in the art could not conclude that Applicant was in possession of the claimed genus of viral fusion proteins that are distinguishable from each other by sensitivity to temperature, ion concentration (other than $H^+$), cell type, or tissue type at the time of the invention.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-9, 11, 13, 16, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Gunther-Ausborn et al (J. Virol. 74(6): 2714-2720, 2000), as evidenced by Junankar et al (Biochimica et Biophysica Acta, Biomembranes (1986), 854(2), 198-206) and Blough (J. Gen. Virol. 12(3): 317-320, 1971).

Gunther-Ausborn taught virosome vesicles comprising phosphatidylcholine, phosphatidylethanolamine, and HA trimers from both influenza strains X-47 and A/Shangdong. These HA fusion proteins have fusion properties that are detectable and are distinct from each other. For example, X-47 HA mediates fusion with a pH optimum of 5.1, whereas A/Shangdong HA mediates fusion with a pH optimum of 5.6. See Fig. 1 on page 2715, and paragraph bridging pages 2715 and 2716. Phosphatidylcholine, phosphatidylethanolamine, are considered to be both liposomal and virosomal lipids because they are components both liposomes and virosomes.

Claims 3 and 4 are included in the rejection because they are interpreted as requiring that the vesicles must be capable of encapsulating the recited substances, not as requiring that the substances must actually be encapsulated in the claimed compositions.

Claim 6 is included because, as evidenced by Junankar, X-47 is distinguished by being sensitive to temperature. It is active only at temperatures above 20°C. As such, it has a "distinct" temperature sensitivity. Note that the rejected claims do not require that this sensitivity must be "distinct" from the temperature sensitivity of A/Shangdong HA.

Claims 13 and 14 are included because phosphatidylcholine, phosphatidylethanolamine are known to occur in the envelopes of influenza viruses (see Blough at e.g. Table 2 on page 319), and so are "virosomal lipids" from influenza virus.

Claim 16 is included because the virosomes bind a cell surface HA-receptor. See page 2715, column 2, lines 12-15.

Claim 38 is included because the composition of Gunther-Ausborn meets all of the physical limitations of the claims, so the functional limitation of a "pharmaceutical composition" is also considered to be met.

Claims 1, 3-8, 16, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Karlsson et al (US Patent 4,859,769) as evidenced by Hoekstra et al (Biochemistry 24: 4739-4745, 1985).

Karlsson taught a liposome equipped with a monoclonal antibody for targeting, a Sendai virus F (fusion) protein, and a cytotoxic drug. See column 17, lines 41-54; paragraph bridging columns 7 and 8. The liposome is considered to be a virosome, due to the presence of the fusion protein, so all of the lipids therein are inherently both liposomal and virosomal lipids.

Claims 3 and 4 are included in the rejection because they are interpreted as requiring that the vesicles must be capable of encapsulating the recited substances, not as requiring that the substances must actually be encapsulated in the claimed compositions.

Claims 5 and 6 are included because Hoekstra showed that Sendai virus fusion was temperature sensitive. See abstract. As such, The F protein has a "distinct" temperature sensitivity.

Claim 38 is included because the composition of Karlsson meets all of the physical limitations of the claims, so the functional limitation of a "pharmaceutical composition" is also considered to be met. Furthermore, the composition is clearly intended for in vivo use.

Claims 1-11, 13-16, and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Walti et al (US Patent 6,210,708).

Walti taught cationic virosomes for delivery of genetic material. See title and column 1, lines 11-16. The virosome membrane contains cationic and/or polycationic lipids, at least one viral fusion peptide and preferably at least one cell-specific marker, advantageously selected from the group consisting of monoclonal antibodies, antibody fragments $F(ab')_2$ and Fab', cytokines, and growth factors, for a selective detection and binding of target cells. See abstract. The virosomes are unilamellar and comprise influenza A/Singapore HA (see column 3, lines 17-20). The virosomes range in size from 120-180 nm. See column 3, lines 20-24. The invention functions based on the

distinct pH sensitivity of the fusion proteins which allow escape from endosomes after endocytosis. See column 6, lines 40-45. The term "fusion peptide, as used by Walti, refers to peptides or proteins capable of inducing and/or promoting a fusion reaction between the virosome membrane and a lipid membrane of the target cell. In most embodiments, it refers to viral spike glycoproteins containing the fusion peptide, particularly to the complete hemagglutinin trimer of viral surface spikes, a monomer thereof, or one or both cleaved subunits, the glycopeptides HA1 and HA2, containing the functional fusion peptide. In another embodiment the term refers to the pure fusion peptide itself, either isolated from natural sources or synthetically produced. In a particularly preferred embodiment, these polypeptides containing the fusion peptide refer to influenza hemagglutinins, especially the one of the A-$H_1$ $N_1$ subtype. See column 8, lines 10-24.

Walti also taught that hemagglutinins from other viruses could be used together with influenza hemagglutinins, exemplifying those from rhabdovirus, parainfluenza virus type III, Semliki Forest virus and togavirus. See column 8, lines 31-37. So Walti discloses virosomes comprising fusion proteins from two distinct viruses.

The virosome also comprises phospholipids such as phosphatidylcholine and phosphatidylethanolamine. See column 10, lines 54-58. Claims 13 and 14 are included because these lipids are present in human cells, and influenza viruses obtain their envelopes from human cells. Absent evidence to the contrary, phosphatidylcholine and phosphatidylethanolamine are present in influenza virus envelopes.

See also claims 1-9, 30-33, 36, 37, and 40.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walti et al (US Patent 6,210,708) in view of Wheeler et al (US Patent 5,976,567).

Walti taught cationic virosomes for delivery of genetic material. See title and column 1, lines 11-16. The virosome membrane contains cationic and/or polycationic lipids, at least one viral fusion peptide and preferably at least one cell-specific marker, advantageously selected from the group consisting of monoclonal antibodies, antibody fragments $F(ab')_2$ and Fab', cytokines, and growth factors, for a selective detection and binding of target cells. See abstract. Cationic lipids include DOTMA, DOTAP, DOSPER and DOGS. See e.g. column 9, line 62 to column 10, line 17 The virosome also comprises phospholipids such as phosphatidylcholine and phosphatidylethanolamine. See column 10, lines 54-58.

Walti did not teach the uncharged lipid POPC or the cationic lipid DDAB.

Wheeler disclosed a variety of lipids that are routinely used as alternatives in making liposomes. Cationic lipids DOTMA, DOTAP, DOSPER, and DOGS were all disclosed as alternatives for DDAB. POPC was disclosed as an alternative to phosphatidyl choline and phosphatidylethanolamine. See column 10, line 39 to column 11, line 32. MPEP 2144.06 indicates that when it is recognized in the art that elements

of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

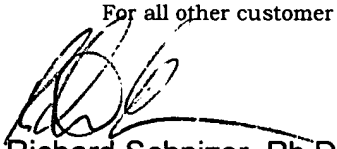
### *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.





Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635